CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64195

BIOEQUIVALENCE REVIEW(S)

10012

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

the state of the s					
Cyclosporine O	ral Solution	SangStat			
100 mg/mL		Menlo Park, CA			
AADA #64-195		Submission Date: 8/14/97			
Reviewer: Moo	Park				
REF PRODUCT	Sandoz's Neoral Oral S	olution ^R , 100 mg/mL strength.			
BE STUDY DESIGN	review by L. Ouderkirk 1. Two-way crossover s	ivalence studies in the original: tudy under fasting conditions. study under nonfasting conditions.			
STUDY RESULTS	Data submitted in the nonfasting in vivo stu	amendment are acceptable. Fasting and dies are acceptable.			
WAIVER	n/a				
.NITIAL: REVIEWER: MOO BRANCH: III		DATE: 1/16/98			
INITIAL: TEAM LEADER: R BRANCH: III	/S/ amakant M. Mhatre, Ph.D	DATE: 1120/98			
INITIAL: DIRECTOR: Dale DIVISION OF BI	P. Conner, Pharm.D.	DATE: 1/20/48			
INITIAL: DIRECTOR OFFICE OF GENE		DATE:			

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 64-195 APPLICANT: SangStat Medical Corp.

DRUG PRODUCT: Cyclosporine Oral Solution, 100 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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Dale P. Conner, Pharm. D. Director, Division of Bioequivalence Office of Generic Drugs Center for Drug Evaluation and Research

Provide de

Cyclosporine Oral Solution

SangStat

100 mg/mL

Menlo Park, CA

AADA #64-195

Submission Date: 8/14/97

Reviewer: Moo Park

Filename: 64195a.897

Review of an Amendment

I. Objective

Review of SangStat's amendment responding to the deficiency letter by the Division of Bioequivalence dated 5/20/97.

II. Background

Mr. Larry Ouderkirk reviewed the original submission of the two in vivo bioequivalence studies conducted under fasting and nonfasting conditions (submission date: 11/21/96; review date: 5/13/97). Mr. Ouderkirk requested additional information for review in the deficiency letter dated 5/20/97. The firm submitted its amendment dated 8/14/97 to answer Mr. Ouderkirk's questions. The amendment was assigned to this reviewer since Mr. Ouderkirk left the Division.

III. Review of the Firm's Responses

SangStat's responses to the deficiency letter were reviewed as follows:

- Q1. The following are in reference to both bioequivalence studies, #18327 conducted under fasting conditions and the food effects study #18328:
 - Q1-a. It is unclear exactly how the standard curves were calculated using the Abbott TD_x system software. Supply an example of the calculation of a typical standard curve, starting from the raw data. An

example should also be furnished of the assay calculations for a typical unknown sample, based on this standard curve.

The firm stated that the analytical method by A1-a. Abbott TDx (fluorescence polarization immunoassay) is currently used by the majority of the 250 US transplant centers to monitor transplant patients cyclosporine blood levels. Abbott stated that the information about the 4PLC Curve Fit Equation utilized by the TDx analyzer is proprietary. information is included in TDx Cyclosporine Monoclonal Whole Blood Assay PMA Supplements P890025/S003 which was approved by FDA. The TDx Analyzer 510(k) submissions were cleared by the FDA. A copy of the Summary of Safety and Effectiveness obtained through Dr. J. Hackett of CDRH/Div. Of Clinical Devices, is attached for reference.

Comment: Firm's response is acceptable.

- Q1-b. The limit of quantitation (loq) of the cyclosporine assay is set at mL and in-house controls at this concentration have been supplied, yet the lowest point of the standard response line is 100 ng/mL. Please comment as to how the linearity of the standard curves were established at concentrations between and 100 ng/mL, and relate the answer to the laboratory's SOP's, and to accepted good laboratory practices.
- A1-b. The Abbott TDx system requires calibration and quality control samples. Abbott's calibrators are six samples at the cyclosporine concentrations of ng/mL in whole blood. The firm used three QC samples from (150, 400 and 800 ng/mL), three QC samples from (65, 193, and 441 ng/mL) and 8 in-house QC samples (0, 25, 50, 150, 500, 800, 1300, and 1500 ng/mL). The firm showed that there is a linear response in the concentration ranges below 150 ng/mL as the linear response observed for the

calibrators. The in-house QC controls at the lower ranges of 25 and 50 ng/mL and the low control sample provided added assurance to support the accuracy and precision of the TDx system at these concentration levels. The TDx Analyzer was approved by the CDRH with a sensitivity of 15 ng/mL of cyclosporine in human serum or plasma.

Comment: Firm's response is acceptable.

- Q1-c. Hard copies of the patient clinical data, including results of the pre-study physical examinations and clinical data collected from the subjects during the studies should be submitted.
- Al-c. The firm submitted the data as requested.

Comment: Firm's response is acceptable.

- Q1-d. Hard copies of the SOP's under which the cyclosporine assays were conducted are required. These SOP's should address the standard procedures for determining the acceptable linearity of the standard curves, and the acceptable quality control of the assays, as well as the procedure for determining the selection of samples for reassay, and the reporting of reassay values. We suggest a tabular format including original value, reason for reassay, reassay value, reported value, and reason for selecting the reported value.
- A1-d. The firm submitted the SOP's as requested.

Comment: Firm's response is acceptable.

- Q1-e. The data on computer diskettes uses an unauthorized format. The following 3 files are needed in ASCII format, suitable for SAS analysis, for each study:
 - File 1 should list the subject, dosing sequence, study period, study treatment, and the plasma drug

concentrations (C1 - Clast).

- File 2 should list the subject, dosing sequence, study period, study treatment, and the PK values (AUCT, AUCI, C_{max} , T_{max} , K_{el} , and T_{y}).
- File 3 should list the SAS codes used for the ANOVA, if available.
- Al-e. The firm submitted the data as requested. This reviewer calculated the PK parameters for the fasting study using the actual sampling times rather than the nominal sampling times. The 90% confidence intervals for the log-transformed AUCT, AUCI, and CMAX were within the acceptable range of 80-125%. The PK parameters and 90% confidence intervals based on the actual sampling times are comparable to the values shown in the original review by L. Ouderkirk.

Table Ale1. ARITHMETIC AND GEOMETRIC MEANS AND TEST/REFERENCE RATIOS

UNDER FASTING CONDITIONS

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

MEAN1=TEST; MEAN2=REF; RMEAN12=T/R RATIO

		MEAN1	SD1	MEAN2	SD2	RMEAN12	
1	PARAMETER				kg sameje l		
- 12	AUCI	13666.63	2387.80	13758.03	2698.01	0.99	
1	AUCT	12963.49	2255.26	13028.62	2530.09	1.00	
ΞÍ٠	CMAX	1684.02	252.27	1711.86	318.58	0.98	
1:	KE	0.08	0.01	0.08	0.01	1.01	
: i:	LAUCI	13460.18	0.18	13494.40	0.20	1.00	
	LAUCT	12769.68	0.18	12783.04	0.20	1.00	
1	LCMAX	1665.20	0.15	1682.95	0.19	0.99	
: :	THALF	8.53	0.59	8.68	0.93	0.98	
. !	TMAX	1.69	0.46	1.80	0.52	0.94	

Table Ale2. 90% CONFIDENCE INTERVALS UNDER FASTING CONDITIONS UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR LSM1=TEST LSMEAN; LSM2=REF LSMEAN; RLSM12=TEST/REF RATIO LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12	
PARAMETER	13662.17	12747 30	0.99	96.26	102.50	
AUCI AUCT	12956.57	13019.28	1.00	96.42	102.62 102.91	
CMAX LAUCI	The second second	13487.20	1.00	96.83	102.96	
LAUCT LCMAX	12773.45	the same of the			103.56	

Comment: Firm's response is acceptable.

- Q2. The following refer only to in vivo bioequivalence study #18327, conducted under fasting conditions:
 - Q2-a. In the pre-study assay validation, the laboratory determined that the samples are stable for 44 days under various storage conditions. In the fasting study #18327, the samples were stored for up to 76 days (6/9/96 to 8/24/96) between collection and assay. Please submit data supporting the stability of the study blood samples for this length of time under the storage conditions used in the study.
 - A2-a. Additional long-term stability data were submitted as summarized in Table A2-a.

Table A2-a. Long-term Stability Data for Bio-Rad QC Samples

QC Samples	Storage Conditions	Storage time	%Initial

Comment: Firm's response is acceptable.

- Q2-b. Table 3 (Summary of QC Results) and Table 4 (Summary of Full QC Runs) do not agree as to which subject samples were assayed on which days. Please correct this apparent discrepancy.
- A2-b. The firm explained that the daily full QC runs were not necessarily conducted at the beginning of each day. Therefore, blood sample analyses were supported by the most recent full run, even if full QC run was conducted the previous day. Once the new daily full QC run is performed, the balance of the study samples assayed in that day are supported by this new full QC run.

Comment: Firm's response is acceptable.

Q2-c. On the assays conducted 8/19, 8/20, 8/21, and 8/22, the in-house QC samples at 50 ng/mL and/or 25 ng/mL gave results outside the acceptable range of actual). Please comment on how the validity of the sample assays was assured on these dates, especially for samples that assayed within these concentration ranges.

A2-c. The firm stated that for the 25 and 50 ng/mL QC samples, the acceptance criterion was The firm further explained that all 0.5 hour study samples were assayed at a level of few hundred ng/mL and 71% of the 36 hour samples were well above 50 ng/mL.

Comment: Firm's response is acceptable.

- Q3. The following refer only to the *in vivo* food effects study, #18328:
 - Q3-a. In the pre-study assay validation, the samples were proved stable for 44 days under various storage conditions. In the food effects study, #18328, the samples were stored for up to 83 days (6/9/96 to 8/31/96) between collection and assay. Data supporting the stability of the blood samples for a time equal to the longest time under the storage conditions used in the study are necessary.
 - A3-a. Please refer to Response #A2-a.

Comment: Firm's response is acceptable.

- Q3-b. On assays conducted 8/27, and 8/28 the in-house QC samples at 25 ng/mL gave results outside the acceptable range (of actual). Please Comment on how the validity of the sample assays was assured on these dates for samples that assayed at concentrations below 50 ng/mL.
- A3-b. The firm stated that for the 25 and 50 ng/mL QC samples, the acceptance criterion was The firm further explained that all 0.5 hour study samples were assayed at a level of few hundred ng/mL and 82% of the 36 hour samples were well above 50 ng/mL.

Comment: Firm's response is acceptable.

- Q3-c. The actual subject blood collection times for the 0.5 hour time point differed significantly from the scheduled time. The report states that the actual times were used to compute the AUC's, but an analysis by the Division of Bioequivalence indicated that the theoretical times were used. Please rectify this apparent discrepancy.
- A3-c. This reviewer calculated the PK parameters for the food study using the actual sampling times rather than the nominal sampling times. Subject #2 and 16 were removed from the calculation because they did not complete all the three periods of dosing. The test/reference ratios for the log-transformed AUCT, AUCI, and CMAX were within the acceptable range of The PK parameters and test/reference ratios based on the actual sampling times are comparable to the values shown in the original review by L. Ouderkirk.

Table A3c1. ARITHMETIC MEANS AND RATIOS FOR CYCLOSPORINE UNDER FASTING/NONFASTING CONDITIONS (UNIT: NG/ML)
UNIT: AUC=NG HR/ML; CMAX=NG/ML; TMAX=HR; KE=1/HR
MEAN1=TEST-FOOD; MEAN2=REF-FOOD; MEAN3=TEST-FAST
RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION

) '도달 그렇고 말 말 말 말 말 말 말 말 말 말 말 보고	، چاک کا کا کا کا کا کا کا محمد محمد م	ه د ه د د د د د د د د د د ۱					RMEAN12
	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEANIZ
PARAMETER						aa aa aa i	eta esti
AUCI	14952.50	2612.01	14929.37	2818.06	13995.55	2704.60	1.00
AUCT	14176.46	2518.61	14173.73	2715.96	13316.43	2585.20	1.00
CMAX	1649.53	322.53	1713.05	364.53	1677.58	302.21	0.96
KE	0.08	0.01	0.08	0.01	0.08	0.01	1.00
LAUCI	14725.93	0.18	14660.08	0.20	13754.38	0.19	1.00
LAUCT	13953.82	0.19	13911.77	0.20	13085.69	0.19	1.00
LCMAX	1621.58	0.19	1676.94	0.21	1653.75	0.17	0.97
THALF	8.27	0.51	8.30	0.51	8.31	0.56	1.00
XAMT	2.13	0.72	1.95	1.20	1.89	0.49	1.09

(Continued)

<u> 14. 6 6 6 7 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 </u>	RMEAN13 RMEAN23
PARAMETER	
AUCI	1.07 1.07
AUCT	1.06 1.06
CMAX	0.98
KE E	1.01 1.00
LAUCI	1.07
LAUCT	1.07 1.06
LCMAX	0.98 1.01
THALF	0.99 1.00
TMAX	1.13 1.03

Table V-Food-PEN-3. LSMEANS FOR CYCLOSPORINE
UNDER FASTING/NONFASTING CONDITIONS (UNIT: NG/ML)
UNIT: AUC=NG HR/ML; CMAX=NG/ML; TMAX=HR; KE=1/HR
LSM1=TEST-FOOD; LSM2=REF-FOOD; LSM3=TEST-FAST
RLSM12=LSM1/LSM2 RATIO

	[강흥 기요 # 기계 : [[[[[[[[[[[[[[[[[[والدالدالدات ليزييان	. '
•		LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23	ĺ
	PARAMETER					1.07	1.07	
	AUCI AUCT		14888.40 14129.98		1.00 1.00	1.07	1.07	
	CMAX LAUCI	1643.42 14669.98	1705.51	1672.24 13704.77	0.96 1.00	0.98 1.07	1.02 1.07	
	LAUCT	13897.84		13036.62	1.00	1.07		:
	LCMAX	1614.9/	1000.02	1049.00				

Comment: Firm's response is acceptable.

IV. Deficiency

None.

V. Recommendation

The two in vivo bioequivalence studies conducted under fasting and nonfasting conditions by Sangstat on its Cyclosporine Oral Solution for Microemulsion, 100 mg/mL strength, lot #D20571M, comparing it to Sandoz's Neoral Oral Solution^R, 100 mg/mL strength, lot #11X8596, have been found acceptable. The studies demonstrate that Sangstat's Cyclosporine Oral Solution for Microemulsion, 100 mg/mL strength, is bioequivalent to the reference product, Sandoz's Neoral Oral Solution^R, 100 mg/mL strength.

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Moo Park, Ph.D. Chemist, Review Branch III Division of Bioequivalence

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Concur:

e: <u>1/20/98</u>

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Dale P. Conner, Pharm.D.

Director

Division of Bioequivalence

File History: Draft (1/6/98) Final (1/16/98)

n. Andre

AADA 64-195

MAY 20 1997

SangStat Medical Corp.
Attention: Hana Berger Moran
1505 Adams Drive
Menlo Park, CA 94205

Dear Madam:

Reference is made to the bioequivalence data submitted on November 21, 1996, for Cyclosporine Oral Solution for Microemulsion.

The Office of Generic Drugs has reviewed the submitted data and the following comments are provided for your consideration:

- 1. The following are in reference to both bioequivalence studies, #18327 conducted under fasting conditions and the food effects study #18328:
 - a. It is unclear exactly how the standard curves were calculated using the Abbott TD_x system software. Supply an example of the calculation of a typical standard curve, starting from the raw data. An example should also be furnished of the assay calculations for a typical unknown sample, based on this standard curve.
 - b. The limit of quantitation (loq) of the cyclosporine assay is set at g/mL and in-house controls at this concentration have been supplied, yet the lowest point of the standard response line is 100 ng/mL. Please comment as to how the linearity of the standard curves were established at concentrations between aL and 100 ng/mL, and relate the answer to the laboratory's SOP's, and to accepted good laboratory practices.
 - c. Hard copies of the patient clinical data, including results of the pre-study physical examinations and clinical data collected from the subjects during the studies should be submitted.
 - d. Hard copies of the SOP's under which the cyclosporine assays were conducted are required. These SOP's should address the standard procedures for determining the

acceptable linearity of the standard curves, and the acceptable quality control of the assays, as well as the procedure for determining the selection of samples for reassay, and the reporting of reassay values. We suggest a tabular format including Original value, Reason for Reassay, Reassay Value, Reported Value, and Reason for selecting the reported Value.

- e. The data on computer diskettes uses an unauthorized format. The following 3 files are needed in ASCII format, suitable for SAS analysis, for each study:
 - File 1 should list the subject, dosing sequence, study period, study treatment, and the plasma drug concentrations (C1 - Clast).
 - File 2 should list the subject, dosing sequence, study period, study treatment, and the PK values (AUCT, AUCI, C_{max} , T_{max} , K_{el} , and T_{u}).
 - File 3 should list the SAS codes used for the ANOVA, if available.
- 2. The following refer only to *in vivo* bioequivalence study #18327, conducted under fasting conditions:
 - a. In the pre-study assay validation, the laboratory determined that the samples are stable for 44 days under various storage conditions. In the fasting study #18327, the samples were stored for up to 76 days (6/9/96 to 8/24/96) between collection and assay. Please submit data supporting the stability of the study blood samples for this length of time under the storage conditions used in the study.
 - b. Table 3 (Summary of QC Results) and Table 4 (Summary of Full QC Runs) do not agree as to which subject samples were assayed on which days. Please correct this apparent discrepancy.
 - c. On the assays conducted 8/19, 8/20, 8/21, and 8/22, the in-house QC samples at 50 ng/mL and/or 25 ng/mL gave results outside the acceptable range of actual). Please comment on how the validity of the sample assays was assured on these dates, especially for samples that assayed within these concentration ranges.

- 3. The following refer only to the *in vivo* food effects study, #18328:
 - a. In the pre-study assay validation, the samples were proved stable for 44 days under various storage conditions. In the food effects study, #18328, the samples were stored for up to 83 days (6/9/96 to 8/31/96) between collection and assay. Data supporting the stability of the blood samples for a time equal to the longest time under the storage conditions used in the study are necessary.
 - b. On assays conducted 8/27, and 8/28 the in-house QC samples at /mL gave results outside the acceptable range (of actual). Please comment on how the validity of the sample assays was assured on these dates for samples that assayed at concentrations below 50 ng/mL.
 - c. The actual subject blood collection times for the 0.5 hour time point differed significantly from the scheduled time. The report states that the actual times were used to compute the AUC's, but an analysis by the Division of Bioequivalence indicated that the theoretical times were used. Please rectify this apparent discrepancy.

As described under 21 CFR 314.96 an action which will amend this application is required, should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301)827-5847. In future correspondence regarding this application, please enclose a copy of this letter.

Sincerely yours,

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Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Cyclosporine
Oral Solution for Microemulsion,
100 mg/mL
AADA #64-195
Reviewer: L.A. Ouderkirk

Sangstat Medical Corp. Menlo Park, California Submission Date: November 21, 1996

Review of In-Vivo Bioequivalence Studies

BACKGROUND:

WP #64195s.N96

Cyclosporine (cyclosporin A) is a potent immunosuppressive antibiotic indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is also indicated for treatment of chronic rejection in patients previously treated with other immunosuppressive agents. The immunosuppressive action of cyclosporine appears mainly to involve inhibition of lymphocytic proliferation and function.

Following oral administration, absorption of cyclosporine from the gastrointestinal tract is variable and incomplete. The time to peak blood cyclosporine concentrations (Tmax) ranged from to

hours in renal transplant patients. The administration of food with cyclosporine decreased the area under the curve (AUC) and peak drug blood concentration (Cmax). A high-fat meal consumed 30 minutes before cyclosporine administration decreased the AUC by 13% and the Cmax by 33%. The effects of a low-fat meal were similar.

Cyclosporine is distributed largely outside the blood volume. In blood, the distribution is concentration-dependent, with approximately 33-47% in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range). Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Cyclosporine is extensively metabolized but there is no major metabolic pathway. The role of metabolites in immunosuppression has not been established.

Cyclosporine oral solution products are marketed by Sandoz Pharmaceuticals as Sandimmune® oral solution, 100 mg/mL and Neoral® oral solution for microemulsion, 100 mg/mL. Because the bioavailability of Neoral® is greater than that of Sandimmune®, the products are not bioequivalent and cannot be used interchangeably without physician supervision.

Cyclosporine oral solution for microemulsion is recommended to be administered diluted with orange or apple juice (but not grapefruit juice, since it may affect the drug's metabolism).

Suggested initial doses are 7-9 mg/kg/day, depending on the indication. The dose is subsequently adjusted to achieve a target cyclosporine blood concentration. The daily dose is recommended to be given in two divided doses (BID), taken on a consistent schedule with regard to time of day and meals.

I. FASTING IN-VIVO BIOEOUIVALENCE STUDY #18327:

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

The bioequivalence study was conducted at

The Principal Investigator was

The analytical portion of the study was conducted at the

The director of the

analytical study was

B. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent before their acceptance into the study. The study protocol was reviewed and approved by an IRB before its initiation.

C. STUDY OBJECTIVE:

The objective of the study was to compare the rate and extent of absorption of the test versus the reference formulation to determine if the test and reference products were bioequivalent when administered to healthy volunteers under fasting conditions as 500 mg single oral doses.

D. STUDY DESIGN:

The study was a random, two-period, two-treatment, two-sequence crossover design using 33 healthy male volunteers.

E. SUBJECT SELECTION CRITERIA:

Subjects selected for the study met the following acceptance criteria:

- 1. Aged 19-55 years.
- Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
- 3. Negative urine screen for alcohol and drugs of abuse.
- 4. No concurrent illness, acute or chronic diseases or history of serious endocrine, cardiovascular, renal, G.I., hepatic, oncologic, or hematopoietic disease.
- 5. No history of tuberculosis, epilepsy, asthma, diabetes, psychosis, or glaucoma.
- 6. No history of alcohol or drug addiction.
- 7. Negative HIV antibody screen.
- 8. No history of lactose intolerance or allergy to milk or other dairy products.

- response history of allergic or adverse cyclosporine or related immunosuppresssant drugs. 9.
- Weight 110-198 lbs and within 15% of ideal for height and frame (Metropolitan Life Insurance Company Bulletin, 10. 1983).

SUBJECT RESTRICTIONS: F.

- No alcohol consumption beginning 48 hours before dosing 1.
- No xanthines beginning 24 hours before dosing in each 2 .
- No Rx drugs beginning two weeks before the study and no OTC drugs beginning 72 hours before the study. 3.
- No participation in a clinical trial within 30 days 4 .
- No treatment with any known hepatic enzyme-inducing or (barbiturates, phenothiazines, 5. cimetidine, etc.) within 30 days before the study. agents
- No donation of plasma within 7 days before the study.
- No donation of one pint or more of blood within 30 days 6. 7.
- No abnormal diets or substantial changes in eating habits within 30 days before the study. 8.

Thirty-six subjects were admitted to the study unit and fasted for 10 hours overnight before dosing. The volunteers were randomly numbered and divided into two dosing groups of equal size. A aliquot of the test or reference product (equivalent to a 500 mg labeled dose of cyclosporine) was mixed in and given to the subjects. An additional was added to each glass, mixed, and also ingested by the subjects. Subjects then continued to fast until 4 hours post-dose, when a standard lunch was served. Water intake was unrestricted, except from one hour before and until two hours after drug administration, when no fluid was permitted other than that needed to administer

Venous blood samples (10 mL) were drawn pre-dose (0 hours) and the dosage form. at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 36 hours post-dose. Within 60 minutes of collection, the blood samples were divided into triplicate aliquots and frozen at or below -15°C . the second set to SangStat set of samples was sent to the Medical Corporation, Menlo Park, California; and the third set was washout period was observed between Phase 1 and 2 dosing.

Blood pressure and pulse measurements were obtained in the morning, before dosing.

H. DRUG TREATMENTS:

- 1. Test Product A: Cyclosporine Oral Solution for Microemulsion, 100 mg/mL, (manufactured for SangStat by Eli Lilly), SangStat Lot #D20571M (Lilly Lot #CT06118), Assayed Potency = 96.6%, Batch Size ., Exp. Date = 12/1/96.
- 2. Reference Product B: Neoral Oral Solution for Microemulsion, 100 mg/mL, (Sandoz), Lot #11X8596, Assayed Potency = 100.3%, Exp. Date = 7/98.
- i. ANALYTICAL:

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M. RESULTS OF FASTING BIOEOUIVALENCE STUDY #18327:

The mean whole blood concentration versus time data for the test and reference products are summarized in **Table 5** and represented graphically in **Figure 1**. Summaries of the arithmetic mean study results and least-squares means study results for pharmacokinetic parameters are given in **Tables 6** and 7, respectively. Test/Reference ratios of the least-squares geometric

TABLE 3 [CONT.]

ASSAY PERFORMANCE SUMMARY

MMARY CONTROLS)

FASTING STUDY #18327

Table 3 - Continued
Summary of Laboratories' Quality Control Results for
SangStat's Bioequivalence Studies - Protocol Number SMC-CSA-35-1

08/20/96	20, 1		보험 방송 화를 모드	
08/23/96	20, 2			
08/20/96	21. 1			
08/23/96	21. 2			
08/20/96	22. 1			
08/23/96	22, 2	_		
08/21/96	23, 1			
08/23/96	23, 2			
08/21/96	24. 1			
08/23/96	24, 2			
08/21/96	25. 1			######################################
08/21/96	25, 1 (repeat)			
08/23/96	25, 2		그들의 생활을 내용하고	
08/21/96	26, 1			
23/96	26, 2	83		
.1796	27, 1			
us/23/96	27, 2			
08/21/96	28, 1			
08/21/96	28, 2 (no show)			
08/21/96	29, 1			
08/23/96	29, 2			
08/21/96	30, I			
08/23/96	30, 2 (no show)			
08/21/96	31, 1			
08/23/96	31, 2			
08/21/96	32, 1			
08/23/96	32, 2			
08/21/96	33, 1			
08/23/96	33, 2			
08/21/96	34, 1			
08/24/96	34, 2			
08/21/96	35, 1			
08/24/96	35, 2			
08/21/96	36, 1			
08/24/96	36, 2			
Mean		65.05	203.53	454.51
Std. Deviation		7.97	11.18	20.01
Min. Value		52.68	166.00	405.89
Max. Value	The second second	76.34	237.88	512.49

n/a Not available

Accepted after running additional QCs as per SOP #4, bad QC sample bottle

Same problem as 22, 1. No repeat performed

Data rejected, repeat after recalibration.

16

No show Patient missed appointment

TABLE 4

ASSAY PERFORMANCE SUMMARY (FULL CONTROL RUNS) FASTING STUDY #18327

Table 4: Summary of Full Quality Control Run for SangStat's Bioequivalence Studies - Protocol Number SMC-CSA-35-1

TABLE 5

FASTING SINGLE-DOSE IN VIVO BIOEOUIVALENCE STUDY #18327

ARITHMETIC MEAN WHOLE BLOOD CYCLOSPORINE CONCENTRATIONS [NG/ML]

VERSUS TIME (CV%) IN 33 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
0	0	0	
0.5	576 (45)	427 (55)	1.35
1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -	1490 (21)	1410 (26)	1.06
	1610 (17)	1640 (21)	0.98
1.5	1640 (17)	1640 (19)	1.00
2	1400 (18)	1400 (18)	1.00
4	1130 (18)	1150 (21)	0.98
6	751 (26)	756 (29)	0.99
8	522 (26)	530 (28)	0.98
10	394 (29)	399 (28)	0.99
12	296 (26)	308 (31)	0.96
	190 (24)	194 (29)	0.98
16	147 (25)	149 (28)	0.99
24	119 (24)	119 (26)	1.00
	69.6 (24)	73.0 (27)	0.95
36	57.2 (24)	58.1 (30)	0.98

FIGURE 1

WHOLE BLOOD CONCENTRATIONS (NG/ML) VERSUS TIME SINGLE-DOSE FASTING STUDY #18327

Mean Blood Cyclosporine Concentrations Versus Time

Linear Scale

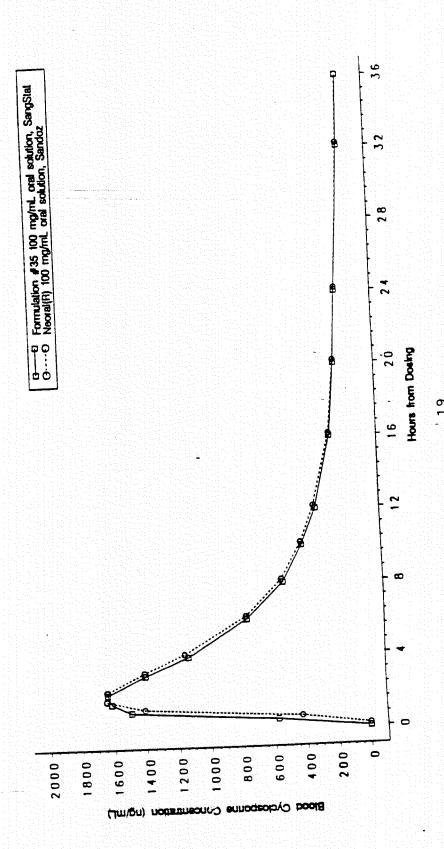


TABLE 6

FASTING SINGLE-DOSE IN VIVO BIOEOUIVALENCE STUDY #18327

ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR (DRUG) IN 33 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	RATIO (A/B)
	33	12971. (18)	33	13023. (20)	1.00
AUCT [ng·hr/mL]	33	9.45	33	9.45	
ln AUCT [ng*hr/mL]	33	12708.	33	12708.	1.00
(Geometric mean)	33	13922. (18)	33	14033. (21)	0.99
AUCI [ng·hr/mL]	33	9.53	33	9.53	
ln AUCI [ng/mL]	33	13767.	33	13767.	1.00
(Geometric mean)	33	1691. (15)	33	1700. (19)	0.99
Cmax [ng/mL] 1n Cmax [ng/mL]	33	7.42	33	7.42	
(Geometric mean)	33	1669.	33	1669.	1.00
Tmax [hr]	33	1.7 (27)	33	1.8 (29)	0.94
K _{el} [1/hr]	33	0.0619 (16)	33	0.0611 (18)	1.01
T _{1/2} [hr]	33	11.5 (16)	33	11.7 (21)	0.98

TABLE 7

FASTING IN VIVO BIOEOUIVALENCE STUDY #18327 LEAST-SOUARES MEANS AND 90% CONFIDENCE INTERVALS FOR PHARMACOKINETIC PARAMETERS

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% CI
AUC(T) [ng•hr/mL]	12968.	12994.	1.00	
ln AUC(T) [ng*hr/mL]	9.455	9.452		
(Geometric mean)	12772.	12734.	1.00	97.2 - 103.3
AUC(I) [ng·hr/mL]	13920.	13999.	0.99	
ln AUC(I) [ng•hr/mL]	9.525	9.525		
(Geometric mean)	13698.	13698	1.00	97.0 - 103.1
Cmax [ng/mL]	1692.	1699.	1.00	
ln Cmax [ng/mL]	7.422	7.421		
(Geometric mean)	1672.	1671.	1.00	96.9 - 103.6
The state of the s	1.7	1.8	0.94	
Tmax [hr]	0.0623	0.0616	1.01	
i _{el} [1/hr] T _{1/2} [hr]	11.4	11.7	0.97	

TABLE 8

ASSAY PERFORMANCE SUMMARY

CONTROLS)

FOOD-EFFECTS STUDY #18328*

Table 3: Summary of Laboratories Quality Control Results for SangStat Medical Corp's Bioequivalence Study - Protocol Number SMC-CSA-35-2

Date of Testing	Subject/Period Number	QC - I 52-78 ng/mL	QC - II 154-232 ng/mL	QC - III 353-529 ng/mL
08/26/96	1, 1			
08/26/96	2. 1			
08/26/96	3, 1			
08/27/96	4. 1			
08/27/96	5, 1			
08/27/96	6, 1			
08/27/96	7, 1			
08/27/96	8. 1			
08/27/96	9, 1			
08/27/96	10, 1			
08/27/96	11, 1			
08/28/96	12. 1			
08/28/96	13. 1			
08/28/96	14, 1			
08/28/96	15. 1			
08/28/96	16. 1			
08/28/96	17. 1.			
08/28/96	18. 1			
08/28/96	19. 1			
08/28/96	20, 1			
08/28/96	21. 1			
08/29/96	1, 2			
08/29/96	2, 2 (no show)			
08/29/96	3. 2			
08/29/96	4, 2			
08/29/96	5, 2			
08/29/96	6. 2			
08/29/96	7, 2			
08/29/96	8, 2			
08/29/96	9, 2			
08/29/96	10. 2			
08/29/96	11, 2			: 교육 (1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
08/29/96	12. 2			
08/29/96	13. 2			
08/29/96	14, 2			
08/29/96	15, 2			

n/a Not applicable

No show Patient missed appointment

TABLE 8 [CONT.]

ASSAY PERFORMANCE SUMMARY

CONTROLS)

FOOD EFFECTS STUDY #18328*

Table 8 - Co	ntinued				
	Summary of			Quality Control	
	SangStat N	Medical Corp	's Bioequiva	lence Study - P	rotocol Number
	SMC-CSA				

08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96	
08/29/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96	
08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96	
08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96	
08/30/96 08/30/96 08/30/96 08/30/96 08/30/96 08/30/96	
08/30/96 08/30/96 08/30/96 08/30/96 08/30/96	
08/30/96) 08/30/96	
08/30/96 08/30/96 08/30/96	
08/30/96	
08/30/96	
<u>08/30/96</u>	
<u>08/30/96</u>	
08/30/96	
<u></u>	
08/30/96	<u>.66</u>
08/30/96	<u> </u>
08/30/96 08/30/96 08/30/96	
08/30/96	<u></u>
08/30/96 <u>1 02.6</u> 7	
08/31/96	
08/31/96	
08/31/96	
08/30/96	
08/31/96	
08/31/96	
08/31/96	
	203.70 460.59
Mean 68.12	6.63 13.77
Std. Deviation 4.34	
Max. Value 77.13 Min. Value 58.40	225.79 493.92 192.24 422.35

n/a Not applicable

No show Patient missed appointment

TABLE 9

ASSAY PERFORMANCE SUMMARY (FULL CONTROL RUNS)

FOOD EFFECTS STUDY #18328*

TABLE 10

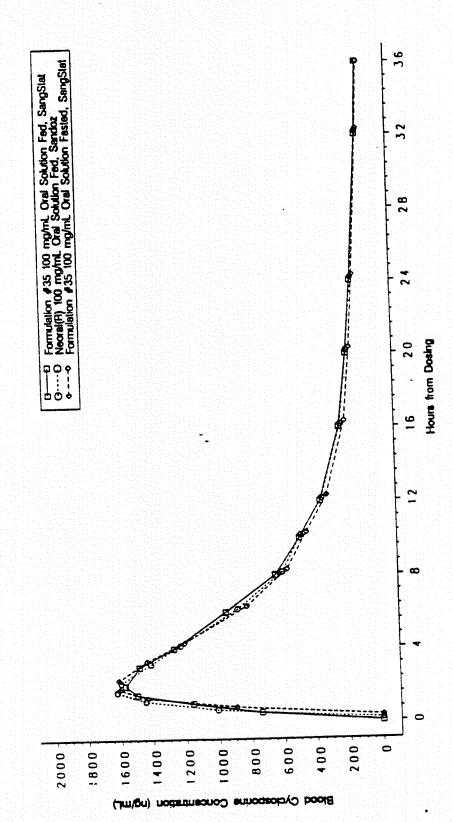
POST-PRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #18328
ARITHMETIC MEAN WHOLE BLOOD CYCLOSPORINE CONCENTRATIONS [NG/ML]
VERSUS TIME IN 19 SUBJECTS (CV%)

TIME (HR)	NON-FASTING TEST TREATMENT A	NON-FASTING REFERENCE TREATMENT B	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
•	00.0		0.00		
0.5	739 (50)	1010 (47)	893 (36)	0.73	0.82
• 1	1160 (40)	1440 (35)	1430 (19)	0.81	0.81
	1490 (27)	1620 (27)	1610 (19)	0.92	0.92
2	1570 (19)	1600 (24)	1610: (18)	0.98	0.98
	40,000%	1410 (25)	1430 (23)	1.05	1.03
	10000	1230 (24)	1200 (25)	1.03	1.06
ه ا	949 (27)	875 (28)	817 (26)	1.08	1.16
C	639 (23)	595 (24)	564 (25)	1.07	1.13
0-	484 (23)	474 (22)	437 (26)	1.02	1,1
-2 -2		343 (26)	312 (25)	1.03	1.13
16	1.0	218 (25)	192 (23)	1.05	1.19
20	173 (24)	170 (25)	151 (22)	1.02	1.15
24	136 (23)	129 (22)	119 (22)	1.05	1.14
32	79 (22)	(1, 77, (23)), (1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	72 (21)	1.03	1.10
3.6	66 (21)	63 (21)	57 (23) 25 25 25 25 25 25 25 25 25 25 25 25 25	1.05	1.16
20	Ш				

FIGURE 2

WHOLE BLOOD CYCLOSPORINE CONCENTRATIONS (NG/ML) VERSUS TIME SINGLE-DOSE FOOD-EFFECTS STUDY #18328

Mean Blood Cyclosporine Concentrations Versus Time Linear Scale



POST-PRANDIAL IN VIVO BIOEQUIVALENCE STUDY #18328
ARITHMETIC MEAN PK VALUES FOR CYCLOSPORINE

								1
PK PARAMETER		FED TEST	* 2	FED REFERENCE TREATMENT B	z	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
	z C	1100 L	10	14306. (19)	20	13614. (19)	1.01	1.07
AUCT [ng*hr/mL]	20	144/3. (10)	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	¥ ¥	20	9.50		
1n AUCT [ng•hr/mL]	20	56 mm 57 mm 5 mm 5 mm 5 mm 5 mm 5 mm 5 m	13				1 01	1.06
(Coometric Mean)	20	14186.	19	14045.	20	13360.		
	5	15574 (18)	19	15331. (19)	20	14571. (19)	1.02	1.0 /
AUCI [ng•hr/mL]	0.2	. `	10	9,62	20	9.57		
In AUCI [ng*hr/mL]	50	9.04	<u>, </u>		20	14328	1.02	1.07
(Geometric Mean)	20	15367.	19	15063	7		60 0	66 0
	2.0	1674. (20)	19	1713. (21)	20	1676. (18)	0.00	
Cmax [ng/mr]		١ -	10	7.42	20	7.41	1 1 1	
ln Cmax [ng•hr/mL]	50		,		c	1652	0.99	1.00
(Geometric Mean)	20	1652	19	1669.	20	**************************************	,	70
	2.0	2.2 (34)	19	1.9 (61)	20	2.0 (27)	1.10	T. T.O
Tmax [hr]	2			117	2.0	0.0611 (12)	1.00	1.01
K ₂₁ [1/hr]	20	0.0619 (17)	19	7771 7790 0	2			1
	20	11.5 (16)	19	11.3 (12)	20	11.5 (13)	r the at	idv and
I 1/2 111		Pariod 2 due to a	resp	respiratory infection, bu	but was	allowed to remer)	7

^{*} Subject #16 missed study Period 2 due to a respir complete Period 3.

TABLE 12

POST-PRANDIAL IN VIVO BIOEQUIVALENCE STUDY #18328
LEAST-SOUARES MEAN PK VALUES FOR CYCLOSPORINE IN 19 SUBJECTS

PK PARAMETER		FED TEST	Z	FED REFERENCE TREATMENT B	Z	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
	Z 0	14433.	19	14444	19	13564.	1.00	1.06
AUCI LINGTIN / mil	19	9.56	19	9.56	19	9.50		N. 100, 100, 100, 100, 100, 100, 100, 100,
rom/rm.6iil ronw ur	19	14186.	1.9	14186.	19	13360	1.00	1.06
(Geometric Mean)	, c	7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	19	15490.	19	14522.	1.00	1.07
AUCI [ng*hr/mb]	10	6.64	19	6	19	9.57		
In Auct the interest) 0 1	15367	19	15214	19	14328	1.01	1.07
(Geometric Mean)			0	7714	19	1680.	0.97	66.0
Cmax [ng/mL]	7	· C 0 0 T	ì		0	17 4		1
ln Cmax [ng•hr/mL]	19	7.40	19		T 2			
(Geometric Mean)	19	1652.	19	1686	19	1670	0.98	0.99
	139	2.2	19	2.0	19	6.1	1.10	1.16
[4/L] X	19	0.0617	19	0.0620	19	0.0609	1.00	1.01
	100	11.5	19	11,3	19	11.6		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1

TABLE 13 COMPARATIVE FORMULATIONS

INGREDIENT	AMOUN'	r Per ML
	SangStat	Neoral*
Cyclosporine, USP	100 mg	100 mg
Dehydrated Alcohol, USP		